Descriptive epidemiology of marine anemia in seapen-reared salmon in southern British Columbia

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Abstract

Marine anemia, also known as plasmacytoid leukemia, is a recently described disease of farmed Pacific salmon in British Columbia. Most of what is known about the disease has been generated through laboratory studies or field investigations of severely affected farms. The goals of this study were to determine the range of the spatial and temporal distribution of naturally occurring marine anemia, identify potential risk factors, and provide an initial description of the impact of the disease on commercial salmon farms in British Columbia. Data were obtained from mail surveys, farm visits, and reviews of clinical and laboratory records. An attempt was made to evaluate negative, as well as mildly, moderately, and severely affected sites. The results showed marine anemia to be widely distributed throughout the major salmon farming regions in British Columbia. The disease was most commonly diagnosed in August and September, when water temperatures were at their seasonal peaks. A wide variety of lineage's and fish sources were associated with the disease. The average mortality rate attributed to marine anemia was 6% (range 2.5% to 11%). The peak occurrence of the disease was associated with a peak in the occurrence of other infectious and inflammatory diseases. The broad demographic distribution of marine anemia, coupled with its endemic nature, indicated that the disease is unlikely to be due to the recent introduction of a new pathogen and that causal factors are widespread in southern British Columbia. It is concluded that the significance of diagnosing marine anemia is not that it is predictive of an impending epidemic of mortality, but that it is an indicator of the general pattern of disease on a farm.

Résumé

Épidémiologie descriptive de l'anémie marine chez le saumon du sud de la Colombie-Britannique élevé en mer

L'anémie marine, également connue comme la leucémie plasmacytoïde, est une maladie décrite depuis peu dans les élevages de saumon du Pacifique de la Colombie-Britannique. La majorité des connaissances concernant cette maladie provient d'études de laboratoires ou d'investigations effectuées dans les élevages sévèrement touchés. Les buts de cette étude était de déterminer, dans l'espace et dans le temps, l'ampleur de la répartition de l'anémie marine telle que rencontrée dans les élevages, d'identifier les facteurs potentiels de risque et de fournir une première description de l'impact de la maladie dans les élevages commerciaux de saumons de Colombie-Britannique. Les données ont été obtenues à partir d'enquêtes postales, de visites des élevages et d'analyses de dossiers cliniques et de laboratoires. Un effort a été fait pour évaluer les sites ou il n'y avait pas de maladie ainsi que les sites légèrement, moyennement et gravement atteints. Les résultats ont montré que l'anémie marine était largement répandue à travers les principales régions d'élevage de saumon de la Colombie-Britannique. La maladie était le plus souvent diagnostiquée en août et en septembre, époque ou la température de l'eau atteint son pic saisonnier. Une grande variété de lignées et de sources de poissons ont été associées à la maladie. La mortalité moyenne associée à l'anémie marine était de 6 % (entre 2,5 % et 11 %). La période de pointe de la maladie était associée avec la fréquence maximale des autres infections et des maladies inflammatoires. La grande distribution démographique de l'anémie marine, couplée avec sa nature endémique, indique que la maladie n'est probablement pas liée à l'introduction récente d'un nouveau pathogène et que les facteurs responsables sont largement répandus dans le sud de la Colombie-Britannique. Il est conclu que l'utilité du diagnostic de l'anémie marine n'est pas de prédire un danger d'épidémie mortelle mais plutôt de servir d'indicateur du modèle général de la maladie dans un élevage.

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Introduction

In 1988, a previously unrecognized disease of farmed chinook salmon (*Oncorhynchus tshawytscha*), known as marine anemia or plasmacytoid leukemia, was found in British Columbia (1). The etiology of this disease has yet to be determined, although the salmon leukemia virus, a recently described retrovirus, has been implicated as the cause of the disease (2,3). Other infectious agents, particularly the microsporidian parasite, *Enterocytozoan salmonis*, have also been suggested as possible causal agents (2). Marine anemia has previously been reported to cause mortality rates as high as 80% to 100% on commercial farms; therefore, it has been considered a threat to the economic viability of the salmon farming industry in British Columbia (4,5). Much of the early information regarding the sources, transmission, and

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effects of marine anemia was based on inferences drawn from laboratory research or studies based on limited samples of moribund fish (6–8).

Although laboratory experiments can provide precise measurements of pathophysiological changes that occur in affected individuals, they are limited in their ability to replicate the complex ecological relationships responsible for maintaining a disease under natural conditions. The primary goals of this study were to determine the distribution of marine anemia, identify potential risk factors, and estimate the impact of the disease on salmon farms in British Columbia. Our objective was to utilize several information sources to acquire a sufficient breadth of observations to generate epidemiological hypotheses regarding the importance of the disease in southern British Columbia and potential causal factors.

Materials and methods

In both the retrospective and prospective portions of this study, the case definition of marine anemia that we utilized was that developed by Stephen and Ribble (1996). Briefly, this definition requires the following: (1) hyperplasia of the interstitial cells of the caudal kidney; (2) >15% of cells in the caudal renal interstitium to be large mononuclear cells, blast cells, and mitotic figures; (3) the presence of mononuclear cell infiltrates, composed primarily of large mononuclear cells and blast cells, in at least one organ other than the spleen or kidney; and (4) no significant signs of granuloma formation or necrosis in the organs examined. The kappa coefficient for intra-observer agreement for this definition is 0.84, a value indicative of excellent diagnostic agreement (9). For retrospectively acquired cases, histological samples were reviewed where possible. Cases that did not have historical tissue samples available for evaluation and lacked sufficient detail in their medical records were excluded from the study due to our inability to ensure they met our case definition.

Spatial, temporal and demographic distribution

Two methods were used to describe the distribution of marine anemia and the demographic features of cases. First, reviews of laboratory and clinical records were conducted to determine the source and seasonality of previous diagnoses of the disease between 1987 and 1992, and to determine the range of ages, sexes, and species that had been associated with the disease. During this time, veterinary services were supplied to the salmon farming industry in British Columbia by veterinarians employed by 4 companies providing feed or pharmaceuticals to the industry. Only 2 of these companies had adequate detail in their clinical records and a client base that reflected the entire industry; therefore, they were the only companies included in this study. The records represented all of the clinical data collected by the companies between 1987 and 1992. Diagnostic submissions from 1987 to 1992 were provided by the primary diagnostic facilities used by the salmon farming industry in British Columbia for the time period of the study; namely the British Columbia Animal Health Centre in Abbotsford, and the Fish Health and Parasitology Section, Pacific Biological Station, Department of Fisheries and Oceans, Nanaimo. Histological tissue sections were reviewed for approximately 90% of the cases supplied by the federal laboratory, but only 10% of the cases obtained from the provincial facility. The original pathological descriptions were evaluated for all cases included in the study for which tissue samples could not be reviewed.

Between 1991 and 1993, 53 farm visits involving 20 different farms in southern British Columbia were conducted. These visits covered all of the major farmed-salmon producing regions of the province. Sites were selected on the basis of accessibility and owner cooperation. At each site, surface moribund fish were collected from chinook salmon pens. Although this sample group has been shown to be potentially biased towards chronically ill fish (10), it represents the pen subpopulation from which farms and previous field research typically collected fish for marine anemia evaluation. Fish were euthanized by cervical severance and subjected to gross pathological examination. Samples of the following organs were collected from each fish and stored in Davidson's solution (11); kidney, heart, liver, spleen, distal colon, pyloric ceca, brain, and retrobulbar tissue. These tissues were later routinely prepared and stained with hematoxylin and eosin for histological examination (11).

Impact and associated variables

A mail survey of salmon farmers was conducted to determine the perceived impact of marine anemia (copies of the survey can be obtained from the 1st author). To satisfy the statistical criteria for detecting the disease at or below 5% prevalence, 45 chinook seafarms were selected using a random number table (12) from a complete list of all licensed sites in British Columbia in 1991. This number represented 41% of operating chinook sites and 44% of the salmon farming companies in the province. The questionnaire was mailed in November 1991, followed by a repeat mailing to nonrespondents in January and March 1992. Areas of inquiry within the survey included the basis used for the diagnosis of marine anemia, demographic and environmental characteristics of the farm, the perceived impact of the disease, and the observed pattern of occurrence.

During the 53 site visits described above, we recorded the water temperature by thermometer at 1 m, 5 m, and 10 m, inside and outside the sampled netpens. The age and length of time at sea were recorded for all fish examined. In addition, the mortality rate for the current week and diagnoses made on dead or moribund fish by the farm's veterinarian were retrieved from the farm and veterinary records.

A subsample of 6 of the 53 farms was selected on the basis of convenience for visits at 2- to 4-week intervals. These farm visits were conducted between May and December in 1992 and 1993. At each visit, all fish that were catchable on the surface and all mortalities from 4 adjacent seapens were retrieved. Fish were subjected to gross and histological examination as described above. To ensure a low proportion of severely decomposed fish, farmers were asked to remove mortalities from study pens the day preceding our visit. Determination of the marine anemia status of dead fish judged to be too autolyzed for reliable histologic examination was based on a diagnostic algorithm utilizing gross

Table 1. Mean prevalence of disease categories observed during mortality surveys on chinook salmon (*Oncorhynchus tshwaytscha*) seafarms in British Columbia

	Category 1[a]	Category 2[b]	Category 3a[c]	Category 3b[c]	Category 4[d]
Marine anemia negative survey	21%	8%	7%	35%	29%
Marine anemia positive survey	26%	33%	14%	9%	13%

Category = associated gross necropsy findings
[a]Fibrinous or granulomatous lesions visible
[b]Signs suggestive of infectious disease process but lacking grossly visible fibrinous or granulomatous lesions including signs typical of gram-negative infection, intestinal inflammation, enlarged visceral organs, inflamed meninges
[c]Any of the following noninfectious process; gastric bloat, victims of algal blooms or predation, precocious maturation, saltwater nonviability ("non-smolts"); Category 3a = all but nonsmolts, Category 3b = nonsmolts only
[d]Open diagnoses or lesions not conforming to categories 1, 2 or 3

lesions. Under typical field conditions, this algorithm has a sensitivity of 71% and a specificity of 91% when histologic diagnosis of marine anemia is used as the gold standard for diagnosis, and an intra-observer kappa value of 0.61 (9). All other necropsied fish were categorized according to the classifications described in Table 1. This classification system was developed as a tool that could be readily employed by farmers and veterinarians to quantify the major causes of death that occur on fish farms, thus allowing for a consistent description of disease on all study farms.

Pearson's correlation coefficient (12) and the chi-squared test of association (12) were used to test the relationship of marine anemia with environmental and disease variables.

Results

Spatial, temporal, and demographic distribution

Prospectively identified, affected fish originated from hatcheries located throughout Vancouver Island and the southern mainland coast of British Columbia. Both well water and surface water hatcheries provided stock to affected farms. Different strains and lineages of broodstock were used by affected farms. Broodstock used by affected farms originated from spawning grounds throughout Vancouver Island, the southern and northern coasts of British Columbia, and the Yukon. Some affected fish were 1st generation offspring of wild salmon, while others were from commercial domesticated stock.

Marine anemia was diagnosed in male, female, and monosexed (fish chemically or physically altered at the egg-stage to be phenotypically female) fish in the prospective portion of our study. The age of affected fish ranged from smolts that had been at sea for approximately 4 mo to broodstock that had been at sea for 4 y.

One hundred and sixty-three of the 182 cases identified retrospectively were farm-reared, monosex, chinook salmon. Isolated cases were reported in clinical and laboratory records in Atlantic salmon (*Salmo salar*) ($n = 2$), farmed coho salmon (*O. kisutch*) ($n = 3$), farmed sockeye (*O. nerka*) ($n = 1$), and wild chinook ($n = 7$). It was not possible to determine if the wild chinook were truly wild or of they were escaped farm fish. A single clinical report described a rainbow trout (*O. mykiss*) with histopathologic features consistent with the disease. However, tissue samples were not available to confirm the diagnosis.

Although cases were found throughout the year, the number of cases of marine anemia detected during the prospective and retrospective investigations peaked in the late summer in each year (Figure 1). The number of visits by veterinarians to salmon farms and the number of submissions to diagnostic laboratories peaked in June and July. This peak in veterinary visits and submissions was due to a marked rise in the number of diagnoses of vibriosis that occurred at that time of the year. The late summer also represented the time of year at which water temperatures began to decline from seasonal maximums. The correlation between the proportion of mortality attributed to marine anemia and the water temperature at a 5-meter depth on the day of mortality surveys was positive, but not statistically significant ($r = 0.31$). A seasonal shift in the pattern of other diseases was also observed during farm visits. Category 1 diagnoses (Table 1) were fewest in September, while the number of category 2 diagnoses peaked near this time of year, corresponding to the pattern observed retrospectively.

Prior to the project, marine anemia had not been diagnosed on 15 of the 23 farms we visited. We later found cases of marine anemia in all but 1 of the 23 farms. The 1 negative farm failed to yield a case on any of the 12 visits conducted over a 6-month period. Marine anemia could not be found in every chinook pen on affected farms, nor was the disease found on every visit to affected sites. On average, 2 visits per site were required before the disease was diagnosed. The frequency of detecting the disease on a farm varied from only once in 10 visits to 11 times in 12 visits.

Impact and associated variables

Responses to the mail survey (38/45) indicated that farmers of chinook salmon in British Columbia considered marine anemia to be a threat to their industry. The

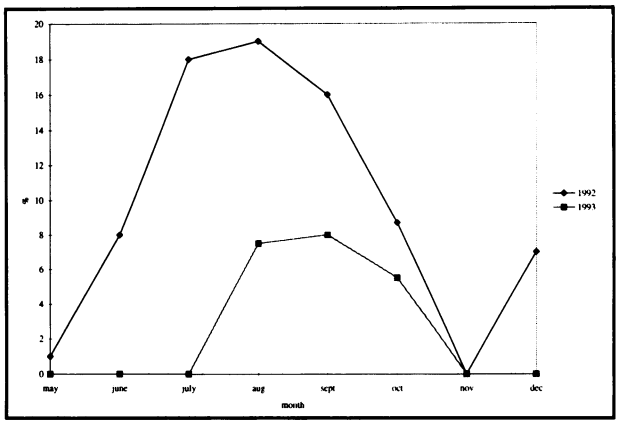

Figure 1. Proportion (%) of dead and moribund fish diagnosed with marine anemia on commercial chinook salmon (*Oncorhynchus tshawytscha*) seafarms in British Columbia (1992–1993).

majority of the respondents (27/38) believed that marine anemia had a significant negative impact on affected farms, primarily by increasing mortality rates and decreasing growth rates. Farmers reported that once marine anemia had been detected on a farm, it was repeatedly diagnosed throughout the remainder of the production cycle and into subsequent years.

Marine anemia had already been diagnosed on 10 of 38 (26%) chinook farms from which responses to the mail survey were received. However, only 6 of these farms used case definitions that were comparable to our diagnostic criteria. Each of these 6 farmers relied upon histopathological evaluation of multiple tissues by experienced fish pathologists to determine the marine anemia status of their farm. On 3 of the other positive farms, the presence of microsporidial parasites in liver tissue imprints was used to make a positive diagnosis of marine anemia. The remaining positive farm used the finding of large, immature, mononuclear cells in Giemsa-stained liver imprints as sufficient evidence for diagnosing marine anemia. Based on our case definition, our survey of fish farmers suggested a farm-level prevalence of marine anemia of 19% (6/32) for operating chinook sites in British Columbia. On follow-up visits to 10 of the farms that participated in the mail survey, we found cases of marine anemia at each farm, including 5 farms that had been classified by the farmers as negative in the mail survey.

The proportion of total mortality attributed to marine anemia during prospective mortality surveys of positive farms ranged from 2.5% to 11% (mean = 6%). The prevalence of marine anemia seen in mortality surveys was positively correlated with pen mortality rates (r = 0.46, $P < 0.05$); however, high mortality rates were recorded on positive and negative farms. The diagnosis of marine anemia was associated slightly more often with decelerating mortality rates (55%, n = 12) than it was with accelerating rates (45%, n = 10).

The pattern of occurrence of the disease varied among our farm visits. A higher proportion of deaths was attributed to category 2 diagnoses on visits when marine anemia was diagnosed than when it was not (chi-squared = 40.62, $P < 0.0001$). In each year of the study, on farms that were monitored for 6 mo, the increase in the number of deaths attributed to category 2 diagnoses coincided with a rise in the proportion of deaths due to marine anemia.

The pattern of mortality seen over 6 mo at the 1 negative farm in the prospective portion of the study was notably different from that at a neighboring positive farm. Located less than 1 km from each other, both farms introduced 1-year-old chinook smolts of similar origin to sea in the spring of 1993. By late August 1993, marine anemia had been diagnosed at 1 of the farms. This farm continued to provide cases of the disease until the end of October. Over the 6-month surveillance period, 80% of the deaths at the negative farm were attributed to predation and inability to adapt to seawater, whereas at the positive farm, category 1 and 2 diagnoses were the most frequent causes of mortality (45%). However, the 6-month cumulative mortality rates at these 2 farms were not significantly different.

Discussion

The wide spatial and demographic distribution of marine anemia seen in this and other studies (13,14) suggests that causal factors for the disease must be ubiquitous in the major seafarming regions of British Columbia. Infectious agents, including the salmon leukemia virus and *Enterocytozoan salmonis*, have been suggested as possible causes of marine anemia (7). The diagnosis of marine anemia soon after fish have been put to sea suggests that either the disease can be rapidly acquired after seawater introduction or fish arrive at seafarms with the disease. The horizontal spread of an infectious agent would be facilitated by the intimate contact and frequent mixing of pens of fish that occurs on seafarms in British Columbia. The use of mixed sources of replacement stock by the industry presents the prospect that a pathogen may initially be restricted to selected groups but, upon entry to the sea, is rapidly disseminated through susceptible populations. In this case, contributing causes or predisposing factors for marine anemia would have to be encountered while fish were still in fresh water. The identification of syndromes histologically indistinguishable from marine anemia in freshwater chinook salmon in California supports the hypothesis that marine anemia is not restricted to the salt water phase of salmon rearing (7,15–17).

The potential source of an infectious agent for marine anemia in fresh water is unclear. Management practices intended to reduce opportunities for horizontal spread of pathogens were used by many of the hatcheries that provided positive stock in this study. The use of well water, which is generally considered free of wild fish and their obligate pathogens, the surface disinfection of eggs, and the separation of stocks and year classes were techniques that many of the hatcheries used to reduce the horizontal spread of pathogens. As vertical transmission can be responsible for the spread of infectious leukemias in other species (18,19), this may be a route for the spread of marine anemia in hatcheries. Circumstantial evidence reported by Kent *et al* (20) supports this hypothesis. In order for a vertically transmitted pathogen to generate the spatial and demographic range of marine anemia seen in this study, it must be widespread in the chinook farming industry in British Columbia.

Broad spatial and demographic distribution, occurrence as an endemic disease, and low mortality rates are all considered to be features that characterize a long-term relationship between a host and an agent, not the recent introduction of a new pathogen (21). Although our results appear to suggest a predisposition to marine anemia for monosexed chinook at sea, it should be noted that, at the time of this study, these fish predominated the industry and were of sufficient value to warrant a veterinary investigation, thus resulting in their being over represented in clinical and laboratory records. Previous studies have associated a more restricted distribution of marine anemia than was seen in this study and have characterized the disease as an epidemic that causes high mortality rates (6,7). These studies differed from our study in that the workers often did not directly examine mortalities when investigating natural occurrence of the disease or they extrapolated the results of laboratory studies to field conditions. However, other factors, such as, the confounding effects of farm management practices, use of varying case definitions, and reliance on different sources of historical information, may also have contributed to the differing descriptions of the epidemiology of marine anemia.

Problems in consistently identifying marine anemia limit our ability to discover the factors that precipitate the disease under natural conditions (9,26). Although this study utilized diagnostic criteria that have been assessed for validity and repeatability, it still provided opportunities for misclassification of cases. Our inability to access equally all segments of penned and wild salmon stocks further limits our ability to describe the natural history of this disease. Until a more reliable method of determining the marine anemia status of fish and farms has been developed, more precise measurement of risk factors will be difficult to achieve.

The association of marine anemia with a variety of immune stimulating factors suggests that immunostimulation may play a role in the pathogenesis of the disease. Peaks in the number of cases of marine anemia in this study occurred at warmer water temperatures, which can facilitate the progression of infectious diseases and allow for a maximum immune response (23). Peaks in the prevalence of marine anemia in mortality surveys were associated with specific and nonspecific signs of inflammatory and infectious diseases within the study population. The only farm at which marine anemia was not detected was also the only site at which infectious and inflammatory disease contributed little to the overall mortality rate. Because one has to rely on postmortem lesions to diagnose marine anemia (6), it has not yet been possible to describe the sequential pathology of this syndrome in individual fish and thus establish the temporal relationship of potential causal factors with the occurrence of the disease. For example, although diagnoses of marine anemia in dead and moribund fish peaked in August and September, current methods for detecting and diagnosing the disease do not allow us to determine the time at which fish were exposed to sufficient causal factors to initiate the disease.

The role of an active immune response and concurrent infection in the pathogenesis of leukemia has been suggested elsewhere (24,25). If immunological cofactors are found to be important in the genesis of marine anemia, new avenues for disease control and prevention may be found. In addition, such a finding would provide an alternative causal hypothesis for the disease in which marine anemia is seen not as a specific retroviral-induced neoplasm, but instead as a nonspecific plasmablast proliferation that can be incited by more than one agent. Current difficulties in differentiating the histological lesions of marine anemia from those of chronic inflammation support this alternative hypothesis (26). Regardless of the speculation regarding the relationship of other infectious diseases and marine anemia (4,6,8), our results suggest that the importance of diagnosing marine anemia on a salmon farm is not that it predicts impending epidemics of mortality, but that it may be an important indicator of the pattern of disease on affected farms.

The environmental conditions created by intensive aquaculture may have facilitated the emergence of marine anemia. Rearing systems used in seapen aquaculture represent a substantial change in the ecology of chinook salmon. Increasing farm sizes, accelerated feeding schedules, stress of shipping and confinement, and suboptimal environmental conditions may all contribute to the susceptibility of farmed salmon to infectious disease and maximize the opportunities for the propagation and maintenance of disease on farms (28,29). In addition, the rapid growth of the chinook farming industry in British Columbia in the 1980s likely contributed to the discovery of marine anemia. By providing large numbers of readily accessible moribund salmon, large scale salmon farming undoubtedly increased the probability of detecting previously unrecognized diseases, including marine anemia. If marine anemia is a "disease of confinement," then its discovery may simply be a reflection of the recent rapid growth of the British Columbia salmon farming industry. CVJ

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BOOK REVIEW

COMPTE RENDU DE LIVRE

Karlen A. ***Man and Microbes. Disease and Plagues in History and Modern Times.*** Putnam, New York, 1995. 270 pp. ISBN 0-87477-759-3. $32.50.

Legionnaire's disease, Lyme disease, AIDS, resurgent tuberculosis, Hantavirus, mad cow disease, verotoxigenic *Escherichia coli*, flesh-eating bacteria, and Ebola virus, these and other new or resurgent infections are attracting banner headlines in a world where microbial disease was thought to have been largely finished by the discovery of antibiotics. What else lurks in the wings?

This book traces the history of plagues to the modern day, emphasizing their role in repeatedly changing the course of human history. The author often makes the point that the changing patterns of human infections are traceable to disruptions of the environment and other novel human activities, and that many human infectious agents are derived from animals, not least among them the human immunodeficiency virus. The story is much more interesting and complex than that, but a chapter devoted to the details of the genetic basis of microbial change is, unfortunately, missing. It is the ability of microbes to acquire, delete, insert, exchange, and rearrange DNA that is central to the story. This, coupled with the staggering number and diversity of microbes in the world, will determine what, besides AIDS, will be the modern Black Death.

As human overpopulation pushes more people to clear the remaining jungles and wild lands of the world, who knows to what endemic infections from animals they will be exposed and how these infections will adapt to their new human hosts? Like Ebola virus, Marburg virus, and Lassa fever, the worst plagues may come from the central African jungles. These infections can potentially quickly reach the major cities of the world by airplane in their incubating hosts, there to undergo rapid amplification and dissemination if the vectors are present. This fascinating story of plagues, both old and new, is told well, although in an overexplanatory, European polymath style with somewhat caricatural and naive judgements. At times, I even wondered if English was the writer's native language.

Although largely intended to terrify a general audience, the book will remind veterinarians to stay humble in the face of microbial infection, to expect new or resurgent infectious diseases in animals, of the continuing importance of their work in controlling zoonotic infections, to support good diagnostic and research microbiology laboratories against cutbacks, and that is was Pasteur who predicted that "Microbes will have the last word."

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